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Applicant:	Ya Fang Liu
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Examiner:	Harle, Jennifer I.
Art Unit:	1654

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Sir:

Transmitted herewith are the following documents:

- [X] **Amendment**
- [X] **Abstract by Dr. F.X. Sureda, "Excitotoxicity and the NMDA receptor"**
- [X] **Copy of PTO-1449 form filed on January 9, 2002**
- [X] **Information Disclosure Statement**
- [X] **PTO 1449 Form with cited reference**
- [X] **Return Receipt Postcard**

Applicant requests a two month extension.

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned at (617) 646-8000, Boston, Massachusetts.

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A check in the amount of **$630.00** is enclosed to cover the following fees: $450.00 for a two month extension fee; and $180.00 for submission of the Information Disclosure Statement. Please charge any underpayment or credit any overpayment to Deposit Account No. 23/2825. A duplicate of this sheet is enclosed.

Respectfully submitted,
Ya Fang Liu, Applicant

By: John R. Van Amsterdam

John R. Van Amsterdam, Reg. No. 40,212
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: L0624.70001US00
Date: July 7, 2005
x07/07/05x

Give on-line comment on the Lisbon meeting or suggest a topic for a future meeting

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EuroSIVA

European Society for Intravenous Anaesthesia

Upcoming Event:

8 th EUROSIVA MEETING
Vienna
Friday 27 May 2005 and Saturday morning 28 May 2005

just before the EUROANESTHESIA meeting

The Royal College of Anaesthetists has accredited the meeting with 5 CME points per day

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Glasgow 6th annual meeting 2002	**Abstracts** **Posters**
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Lisbon 7th annual meeting 2004	**Abstracts** **Posters**

Friday 31 March 2000 (8.15-18.00 h)

Current concepts on pharmacokinetic/pharmacodynamic modelling
Chairman: G Kenny (UK)

Physiological pharmacokinetic modelling
A Hoeft(Germany)

Response surface modelling of drug interaction
Charles Minto (Australia)

Effect site modelling and its application in TCI
E Mortier (Belgium)

Advanced delivery and monitoring techniques: an update
Chairman: J Vuyk (The Netherlands)

The development and future of TCI
I Glen (UK)

Closed loop control of intravenous agents
G Kenny (UK)

Intravenous anaesthesia and CNS monitoring
S Schraag (Germany)

Intravenous anaesthesia and old age
Chairman: F Servin (France)

(Patho)physiology of ageing and drug action
S.Legrain (France)

Propofol pharmacokinetic/dynamic changes with age
T Schnider (Switzerland)

Dosing strategies in the elderly
Telmage Egan(USA)

Current concepts of outpatient anaesthesia
Chairman: L Barvais (Belgium)

PK/PD for outpatient anaesthesia
J Raeder (Norway)

Sedation for locoregional anaesthesia
A Holas (Austria)

Postoperative management of outpatient anaesthesia
K Korttila (Finland)

Saturday 1 April

NMDA receptor and anaesthetic action
Chairman: FHM Engbers (The Netherlands)

NMDA receptors and general anaesthetic action
H Flohr (Germany)

NMDA receptors and μ-opioid receptor

State of the art in neuromuscular blockade
Chairman: A Borgeat (Switzerland)

Perioperative complications of NMB
J Viby-Mogensen (Denmark)

NMBA for fast tracking anaesthesia
H Mellinghof (Germany)

relationships
H.Adams (Germany)

Excitotoxicity and the NMDA receptor
FX Sureda (Spain)

Anaphylaxis and NMBA
MC Laxenaire (France)

Excitotoxicity and the NMDA receptor

Dr. F. X. Sureda

1.- The concept of excitotoxicity.

Excitotoxicity, which was first described by Olney in the nineteen-seventies[1], involves the activation of glutamate receptors in the central nervous system (CNS). Glutamate, an excitatory amino acid, activates different types of ion channel-forming receptors (ionotropic) and G-protein-coupled receptors (metabotropic) to develop their essential role in the brain. However, high concentrations of glutamate, or neurotoxins acting at the same receptors, cause cell death through the excessive activation of these receptors. In physiological conditions, the presence of glutamate in the synapse is regulated by active, ATP-dependent transporters in neurones and glia. For instance, in CNS ischaemia a decrease in the levels of glucose causes a decrease in ATP production, leading to an impairment of glutamate uptake. Moreover, the membrane potential of presynaptic neurones is lost and efflux of excitatory amino acids occurs, contributing to the excessive activation of post-synaptic glutamate receptors[2].

2.- The glutamate receptors.

As pointed out above, glutamate and other amino acids can activate both ionotropic and metabotropic receptors (for review, 3). The latter are subdivided into three main families, and can be coupled to phospholipase C (PLC) or to adenylyl cyclase (AC). The ion channel-forming receptors are subdivided into three receptor classes that are named by their selective agonists: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, kainate receptors and NMDA (N-methyl-D-aspartic acid) receptors. AMPA and kainate receptors trigger rapid excitatory neurotransmission in the CNS by promoting entry of Na^+ into neurones. However, a subset of neurones in the hippocampus, cortex and retina express AMPA receptors that are also permeable to Ca^{2+}. NMDA receptors are associated with a high-conductance Ca^{2+} channel that in resting, non-depolarising conditions is blocked by Mg^{2+} in a voltage-dependent manner. Their activation is secondary to AMPA- or kainate-receptor activation, which depolarises the neurone, allowing the release of the Mg^{2+} blockade.

3.- Role of NMDA receptors in the excitotoxic process.

The physiological role of the NMDA receptor seems to be related to synaptic plasticity. In addition, working together with metabotropic glutamate receptors, it ensures the establishment of long-term potentiation (LTP), a process believed to be responsible for the acquisition of information. These functions are mediated by calcium entry through the NMDA receptor-associated channel. Calcium activates a number of Ca^{2+}-dependent enzymes that influence a wide variety of cellular components, like cytoskeletal proteins or second- messenger synthases. However, overactivation at NMDA receptors triggers an excessive entry of Ca^{2+}, initiating a series of cytoplasmic and nuclear processes that promote neuronal cell death. For instance, Ca^{2+}-activated proteolytic enzymes, like calpains, can degrade essential proteins. Moreover, Ca^{2+}/calmodulin kinase II (CaM-KII) is activated, and a number of enzymes are phosphorylated, which increases their activity. Transcription factors such as c-Fos, c-Jun or c-Myc are also expressed. Furthermore, Ca^{2+}-dependent endonucleases can degrade DNA. All these mechanisms, together with enhanced oxidative stress (see below) can induce cell death through necrosis as well as apoptosis, a type of programmed cell death that is described in several neurodegenerative diseases.

4.- Oxidative stress in the excitotoxic process.

Mitochondria have an important role in the regulation of the intracellular calcium concentration. An increased entry of Ca^{2+} into the mitochondria is believed to enhance the mitochondrial electron transport, increasing the production of reactive oxygen species (ROS) such as $^{\cdot}O_2^-$. Although mitochondria are the main source of ROS in the excitotoxic process, there are many enzymatic systems that primarily or secondarily increase the presence of these compounds in the CNS[4]. Calcium-dependent enzymes convert xanthine dehydrogenase to xanthine oxidase, leading to the production of $^{\cdot}O_2^-$ and H_2O_2. Moreover, Ca^{2+} activates the enzyme phospholipase A_2 (PLA_2), which leads to the production of arachidonic acid, which in turn, is transformed by cyclooxygenases, increasing the formation of $^{\cdot}O_2^-$. Calcium also activates NO-synthase, increasing the presence of $^{\cdot}NO$ in the neurone and also in surrounding areas. $^{\cdot}NO$ has a double effect, since it activates guanylylcyclases and also reacts with $^{\cdot}O_2^-$ to form the highly toxic compound peroxynitrite ($ONOO^-$). This is a strong oxidizing agent that causes nitration in proteins and oxidation of lipids, proteins and DNA, leading to a form of cell death that has the characteristics of apoptosis. Lipid peroxidation alters the structure of lipidic membranes, and leakage occurs in the cytoplasmic membrane. Apart from the loss of ionic gradients, release of glutamate from presynaptic terminals is enhanced, which exacerbates these effects.

5.- Involvement of excitotoxicity in neurodegenerative diseases.

Excitotoxicity has been related to several acute neurological disorders, such as epileptic convulsions, in which excitatory synapses become over active. In ischaemic stroke and in post-traumatic lesions, the involvement of excitotoxicity is well established. As mentioned above, in these particular pathological situations a decrease in ATP production evokes glutamate release through depolarisation of presynaptic terminals. In neurodegenerative disorders like Parkinson's or Alzheimer's disease, Huntington's chorea or amyotrophic lateral sclerosis (ALS), a role for excitotoxicity has also been postulated. Moreover, drugs that block NMDA or other glutamate receptors, as well as compounds that decrease glutamate release, attenuate some of the pathological symptoms in experimental models of acute and chronic neurodegenerative diseases.

6.- Development of NMDA antagonists as neuroprotective drugs.

Due to the relevance of the neurodegenerative diseases mentioned above and the lack of effective treatment, research in the field of NMDA antagonists in the last decade has been extremely active. However, glutamate has a very important role in the CNS, and several clinical trials have been abandoned due to psychomimetic or cardiovascular side-effects. Although the search for compounds that could act on NMDA receptors continues, other strategies like glutamate-release inhibitors or non-NMDA receptor antagonists are leading the research in the field of neuroprotective drugs[5].

References.

[1] Olney JW., Sharpe LG., Feigin RD. J. Neuropathol. Exp. Neurol., 31:464-88, 1972.

[2] Dirnagl U., Iadecola C., Moskowitz MA. Trends Neurosci., 22:391-397, 1999.

[3] Michaelis EK. Prog. Neurobiol., 54:369-415, 1998.

[4] Greene JG., Greenamyre JT. Prog. Neurobiol., 48:613-634, 1996.

[5] Baudy RB. Exp. Opin. Ther. Patents 6:983-1033, 1996.